Official Protocol Title:	A Pivotal Phase 3 Randomized, Placebo-controlled Clinical Study to Evaluate the Efficacy and Safety of the sGC Stimulator Vericiguat/MK-1242 in Adults With Chronic Heart Failure With Reduced Ejection Fraction
NCT number:	NCT05093933
Document Date:	25-Jan-2024

TITLE PAGE

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Protocol Title: A Pivotal Phase 3 Randomized, Placebo-controlled Clinical Study to Evaluate the Efficacy and Safety of the sGC Stimulator Vericiguat/MK-1242 in Adults With Chronic Heart Failure With Reduced Ejection Fraction

Protocol Number: 035-03

Compound Number: MK-1242

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	Not applicable
EU CT	2022-500881-80-00
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WHO	Not applicable
UTN	Not applicable
IND	116,743

Approval Date: 25 January 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 03	25-JAN-2024	The purpose of this amendment is to update the SAP.
Amendment 02	01-AUG-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity change and update to the address.
Amendment 01	28-JAN-2022	The purpose of this amendment is to provide country-specific adverse event reporting requirements for sites in Germany.
Original Protocol	14-JUL-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment:

The purpose of this amendment is to update the SAP.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 9.1, Statistical Analysis Plan Summary	Modified IA by removing the number of required events for primary endpoint and triggering IA and final analysis based on number of CV deaths.	This change was made to address new data. The observed ratio of CV death rate to the primary endpoint event rate is lower than projected due to the slower than anticipated event rate for CV deaths. Therefore, the IA and final analysis triggers will be based solely on the number of CV death events.

Description of Change Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Synopsis, Duration of participation	Updated the definition for duration of participation.	Refer to rationale for Section 9.1.
Section 1.3.2, Schedule of Activities – Participants Who Prematurely Discontinue Study Intervention	Specified that study contacts should be calculated relative to randomization.	To clarify when to initiate safety follow-up contact and how to calculate timing of safety follow-up contacts for participants who prematurely discontinue study intervention.
Section 4.1, Overall Design	Updated timing of Final Visit.	Refer to rationale for Section 9.1.
Section 4.4.2, Primary Completion Date	Updated definition of Primary Completion Date.	Refer to rationale for Section 9.1.
Section 6.4, Study Intervention Compliance	Rephrased guidance on study intervention compliance for instance of protocol-specified study intervention interruptions	To clarify range of compliance not considered to be a protocol deviation.
	Rephrased timing of assessments of compliance.	To clarify at which visits compliance will be assessed.
Section 6.6, Dose Modification (Titration)	Added additional guidance for initiation, up-titration, and restart of study intervention.	To clarify that mean SBP should be ≥100 mmHg for initiation, up-titration, or restarting study intervention.

Description of Change **Section Number and Name**	**Description of Change**	**Brief Rationale**
Section 6.6.1, Resumption of Study Intervention Following Interruption	Rephrased considerations for restarting study intervention.	To clarify procedure for restarting study intervention after interruption for reasons other than intolerability.
Section 7.1, Discontinuation of Study Intervention	Clarified discontinuation criteria related to eGFR.	To provide additional guidance for participants requiring short-term or chronic dialysis during the study.
	Added language allowing participants to restart study intervention.	To clarify that participants are now allowed to restart study intervention after Sponsor consultation.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Added a footnote to Table 3.	To clarify the regulatory reporting requirements for events meeting serious criteria that have been determined not to meet endpoint criteria.
Section 8.6.1, Blood Collection for Plasma MK-1242	Added that date and time of sample collection and last dose of study intervention is required.	To clarify documentation requirements are for all PK samples.
Section 8.11.3, Participants Who Prematurely Discontinue Study Intervention	Clarified follow-up contact scheduling and timing.	Refer to rationale for Section 1.3.2.
Section 9.6.1 Efficacy Analyses	Updated definition of primary completion date	Refer to rationale for Section 9.1.
Section 9.7, Interim Analyses	Modified timing of efficacy IA.	Refer to rationale for Section 9.1.
Section 9.8, Multiplicity	Updated criteria for IA success.	Refer to rationale for Section 9.1.
Section 9.9, Sample Size and Power Calculations	Clarified the power of the trial is based on the CV death endpoint.	The power to detect a difference in the primary endpoint is revised to reflect the result of sizing the trial based on the CV deaths.
Section 10.8, Determination of ALBI Grade	Corrected ALBI Grade 2 score.	To align ALBI score with previous protocol clarification letter correction.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Pivotal Phase 3 Randomized, Placebo-controlled Clinical Study to Evaluate the Efficacy and Safety of the sGC Stimulator Vericiguat/MK-1242 in Adults With Chronic Heart Failure With Reduced Ejection Fraction

Short Title: Vericiguat Outcomes Study in HFrEF

Acronym: VICTOR

Hypotheses, Objectives, and Endpoints:

In adults with chronic heart failure with reduced ejection fraction receiving guideline-directed medical therapy for heart failure:

Primary Objective	**Primary Endpoint**
Objective: To evaluate the efficacy of vericiguat compared with placebo on reducing the risk of cardiovascular death or heart failure hospitalization Hypothesis (H1): Vericiguat is superior to placebo in reducing the risk of cardiovascular death or heart failure hospitalization.	Time from randomization to the first event of cardiovascular death or heart failure hospitalization
Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate the efficacy of vericiguat compared with placebo on reducing the risk of cardiovascular death Hypothesis (H2): Vericiguat is superior to placebo in reducing the risk of cardiovascular death.	Time from randomization to cardiovascular death

Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the risk of heart failure hospitalization Hypothesis (H3): Vericiguat is superior to placebo in reducing the risk of the first event of heart failure hospitalization. Hypothesis (H4): Vericiguat is superior to placebo in reducing the risk of all heart failure hospitalization events.	-Time from randomization to the first event of heart failure hospitalization -Time from randomization to all heart failure hospitalization events
Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the risk of all-cause mortality or heart failure hospitalization Hypothesis (H5): Vericiguat is superior to placebo in reducing the risk of all-cause mortality or heart failure hospitalization.	Time from randomization to the first event of all-cause mortality or heart failure hospitalization
Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the risk of all-cause mortality Hypothesis (H6): Vericiguat is superior to placebo in reducing the risk of all-cause mortality.	Time from randomization to all-cause mortality
Objective: To evaluate the safety and tolerability of vericiguat compared with placebo	-Selected nonserious adverse events -Serious adverse events -Events of clinical interest

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Ejection fraction abnormal
Population	Participants with chronic HRrEF
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects, Care Provider, Investigator, Outcomes Assessor, and Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 43 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 6000 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Vericiguat	MK-1242 (vericiguat)	2.5 mg, 5 mg, and 10 mg	2.5 mg, 5 mg, or 10 mg QD	Oral	Titration: 2.5 mg titrated to 5 mg titrated to 10 mg / Day 1 until end of treatment	Test Product
Placebo	Placebo for MK-1242 (vericiguat)	0 mg matching placebo for 2.5 mg, 5 mg, and 10 mg	0 mg QD	Oral	Sham Titration: 0 mg / Day 1 until end of treatment	Placebo

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-1242 and BAY 1021189.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Study participants will participate in the study for a median follow-up of approximately 25 months from the time the participant provides documented informed consent through the Final Contact. After a screening phase of up to 30 days, each participant will receive assigned intervention until the required number of CV deaths (approximately 590) are observed in this study. All participants will be followed for efficacy endpoints until the end-of-study. After the end of treatment, each participant will be followed for 14 days for safety.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Events Committee	Yes

Study governance considerations are outlined in Appendix 1.

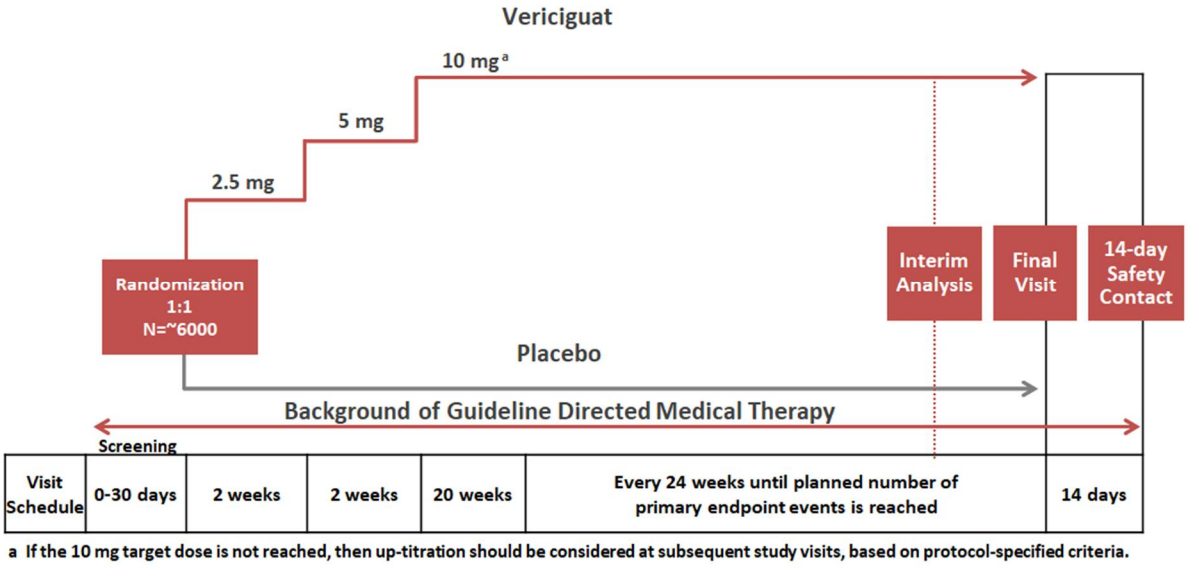
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



a If the 10 mg target dose is not reached, then up-titration should be considered at subsequent study visits, based on protocol-specified criteria.

1.3 Schedule of Activities

1.3.1 Schedule of Activities – All Participants

Study Period:	**Screening**	**Intervention**						**Follow-up**	**Notes**
Visit Number/Title:	**1 Screening**	**2 Randomization**	**3**	**4**	**5**	**n**	**Final Visit**	**14-day Safety Contact**	Visits 1 and 2 may occur on the same day (see Sec. 8.11.1.2 and 8.11.2.1). Visit dates should be calculated relative to Randomization (Day 1). For participants who prematurely discontinue study intervention, see Sec. 1.3.2.
Scheduled Hour, Day, Week, etc, and Window:	**Days -30 to 1**	**Day 1**	**Day 14 ±4 days**	**Day 28 ±4 days**	**Week 24 ±14 days**	**Q24W ±14 days**	**After Primary Completion Date**	**14 days After Last Dose**	
Administrative Procedures									
Informed Consent	X								Participants may provide documented consent for an optional Target Screening blood draw before the Screening Visit (Sec. 8.11.1.1).
Informed Consent for Future Biomedical Research	X								Participation in FBR is optional.
Echocardiogram	X								If needed for inclusion criterion No.6 (Sec. 5.1).
Inclusion/Exclusion Criteria	X	X							
Participant Identification Card	X	X							Visit 2: Add randomization number.
Medical History	X	X							Screening: Collect participant demographics. Visit 2: Update with any changes since screening.
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	See Sec. 6.5 for reporting requirements.
Intervention Randomization		X							

Study Period:	**Screening**	**Intervention**						**Follow-up**	**Notes**
Visit Number/Title:	**1 Screening**	**2 Randomization**	**3**	**4**	**5**	**n**	**Final Visit**	**14-day Safety Contact**	Visits 1 and 2 may occur on the same day (see Sec. 8.11.1.2 and 8.11.2.1). Visit dates should be calculated relative to Randomization (Day 1). For participants who prematurely discontinue study intervention, see Sec. 1.3.2.
Scheduled Hour, Day, Week, etc, and Window:	**Days -30 to 1**	**Day 1**	**Day 14 ±4 days**	**Day 28 ±4 days**	**Week 24 ±14 days**	**Q24W ±14 days**	**After Primary Completion Date**	**14 days After Last Dose**	
Vericiguat/Placebo Administration/ Dispensing		X	X	X	X	X			Complete after Vital Signs and Dose Assessment and Modification.
Study Intervention Compliance			X	X	X	X	X		
Efficacy Procedures									
Clinical Events Assessment			X	X	X	X	X	X	Can be requested at any time during the study.
NYHA Classification	X	X	X	X	X	X	X		
EQ-5D-5L		X			X	Q48W	X		Perform EQ-5D-5L before KCCQ.
KCCQ		X			X	Q48W	X		Complete the QoL questionnaires prior to performing any visit procedure. Visit 2: Complete after IRT randomization and before any other procedures. After V5, EQ-5D-5L, and KCCQ will be performed at every other visit (ie, every 48 weeks).
Vital Status		◄———	———	———	———	———	———►	X	Can be done at any time when vital status is in question.
Safety Procedures									
Full physical examination including height	X						X		Height is not required at the Final Visit.
Directed Physical Examination					X	X			
Vital Signs (pulse rate, sitting BP, weight)	X	X	X	X	X	X	X		Visit 2: BP and pulse rate measurements are required before and 2 h ± 0.5 h after dosing. See Sec. 8.3.2.

Study Period:	**Screening**	**Intervention**						**Follow-up**	**Notes**
Visit Number/Title:	**1 Screening**	**2 Randomization**	**3**	**4**	**5**	**n**	**Final Visit**	**14-day Safety Contact**	Visits 1 and 2 may occur on the same day (see Sec. 8.11.1.2 and 8.11.2.1). Visit dates should be calculated relative to Randomization (Day 1). For participants who prematurely discontinue study intervention, see Sec. 1.3.2.
Scheduled Hour, Day, Week, etc, and Window:	**Days -30 to 1**	**Day 1**	**Day 14 ±4 days**	**Day 28 ±4 days**	**Week 24 ±14 days**	**Q24W ±14 days**	**After Primary Completion Date**	**14 days After Last Dose**	
Dose Assessment and Modification		X	X	X	X	X			Perform at any visit when BP is assessed. See Sec. 8.3.3.
12-lead ECG		X							Visit 2: Perform predose.
AE/SAE review	X	X	X	X	X	X	X	X	See Sec. 8.4 for limitations to AE reporting.
Clinical Laboratory Assessments									
Urine or Serum hCG (WOCBP only; per local requirements)	X	X		In addition to site testing at every visit, urine pregnancy testing will be performed Q4W at home using site-provided kits until 1 month after the last dose of study intervention					Serum test is required if urine test cannot be confirmed as negative See Sec. 8.3.6.
Serum Follicle-Stimulating Hormone (FSH) - (WONCBP only)	X								Perform 2 tests 2-3 weeks apart if required to confirm menopause status (Appendix 5).
Creatinine (eGFR)	X								A historical result collected within 30 days before randomization is acceptable. ALBI score must be calculated at Screening Visit (Appendix 8).
Albumin	X								
Total bilirubin	X								
ALT	X								
AST	X								
Hematology		X		X	X	X	X		
Chemistry		X		X	X	X	X		
Liver Function Tests		X			X	X	X		
NT-proBNP	X	X			X	X	X		Screening: A historical result collected within 30 days before randomization is acceptable.

Study Period:	**Screening**	**Intervention**						**Follow-up**	**Notes**
Visit Number/Title:	**1 Screening**	**2 Randomization**	**3**	**4**	**5**	**n**	**Final Visit**	**14-day Safety Contact**	Visits 1 and 2 may occur on the same day (see Sec. 8.11.1.2 and 8.11.2.1). Visit dates should be calculated relative to Randomization (Day 1). For participants who prematurely discontinue study intervention, see Sec. 1.3.2.
Scheduled Hour, Day, Week, etc, and Window:	**Days -30 to 1**	**Day 1**	**Day 14 ±4 days**	**Day 28 ±4 days**	**Week 24 ±14 days**	**Q24W ±14 days**	**After Primary Completion Date**	**14 days After Last Dose**	
Pharmacokinetics/Biomarkers									
Blood for Genetic Analysis		X							Visit 2: Collect predose. See Sec. 8.8.1.
Blood for Exploratory Biomarker Research		X			X				Visit 2: Collect predose. See Sec. 8.9 for use of leftover sample.
PK sample collection		X		X	X	Q48W	X		Visit 2: Collect predose. After Visit 5, PK samples will be collected at every other visit (ie, every 48 weeks).

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EQ-5D-5L=EuroQol Group 5-Dimensional, 5-level Questionnaire; FBR=future biomedical research; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; IEC=Independent Ethics Committee; IRB=Institutional Review Board; KCCQ=Kansas City Cardiomyopathy Questionnaire; NYHA=New York Heart Association; NT-proBNP=N-terminal pro-brain natriuretic peptide; PK=pharmacokinetic; Q24W=every 24 weeks; Q4W=every 4 weeks; Q48W=every 48 weeks; SAE=serious adverse event; V=Visit; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

Country-specific requirements are noted in Appendix 7.

1.3.2 Schedule of Activities – Participants Who Prematurely Discontinue Study Intervention

Study Period:	**Premature Discontinuation**	**Follow-up**			**Notes**
Visit Number/Title:	**Study Intervention Discontinuation**	**14-day Safety Contact**	**Follow-up Contact**	**Final Contact**	
Scheduled Hour, Day, Week, etc., and Window:	**Premature Discontinuation of Study Intervention**	**14 Days After Last Dose**	**Q24W ±14 days**	**After Primary Completion Date**	Visit/Contact dates should be calculated relative to Randomization (Day 1).
Administrative Procedures					
Prior/Concomitant Medication Review	X	X	X	X	See Sec. 6.5 for reporting requirements.
Study Intervention Compliance	X				
Efficacy Procedures					
Clinical Events Assessment	X	X	X	X	Can be requested at any time during the study.
NYHA Classification	X				
EQ-5D-5L	X				Perform EQ-5D-5L before KCCQ. Complete the QoL questionnaires prior to performing any visit procedure.
KCCQ	X				
Vital Status	◄———	———	———►	X	Can be conducted at any time when vital status is in question.
Safety Procedures					
Full physical examination	X				
Vital Signs (pulse rate, sitting BP, and weight)	X				See Sec. 8.3.2.
AE/SAE review	X	X			
Clinical Laboratory Assessments					
Urine or Serum hCG (WOCBP only; per local requirements)	X	Use home pregnancy kit 1 month after last dose			Serum test is required if urine test cannot be confirmed as negative. Perform urine pregnancy testing at home using site-provided kit 1 month after the last dose of study intervention. See Sec. 8.3.6.
Hematology	X				
Chemistry	X				
Liver Function Tests	X				

Study Period:	Premature Discontinuation	Follow-up			Notes
Visit Number/Title:	Study Intervention Discontinuation	14-day Safety Contact	Follow-up Contact	Final Contact	
Scheduled Hour, Day, Week, etc., and Window:	Premature Discontinuation of Study Intervention	14 Days After Last Dose	Q24W ±14 days	After Primary Completion Date	Visit/Contact dates should be calculated relative to Randomization (Day 1).
NT-proBNP	X				
Pharmacokinetics/Biomarkers					
Blood for Exploratory Biomarker Research	X				Required only if participant discontinues study intervention before Visit 5.
PK sample collection	X				Required only if participant has received study intervention within the previous 2 weeks.

AE=adverse event; BP=blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EQ-5D-5L=EuroQol Group 5-Dimensional, 5-level Questionnaire; hCG=human chorionic gonadotropin; KCCQ=Kansas City Cardiomyopathy Questionnaire; NT-proBNP=N-terminal pro-brain natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetic; Q24W=every 24 weeks; SAE=serious adverse event; V=Visit; WOCBP=women of childbearing potential.

2 INTRODUCTION

Vericiguat is a novel oral sGC stimulator indicated in the US to reduce the risk of CV death and HFH following a hospitalization for HF or need for outpatient IV diuretics in adults with symptomatic chronic HF and ejection fraction less than 45%. This study will evaluate the efficacy of vericiguat in participants with chronic HFrEF, specifically those with symptomatic chronic HF with an ejection fraction of 40% or less who have not had a recent hospitalization for HF or need for outpatient IV diuretics.

2.1 Study Rationale

Heart failure is a leading cause of CV morbidity and mortality and constitutes a major public health problem worldwide. Despite treatment with GDMT, patients with chronic HFrEF remain at high risk for progressive decline with recurrent HFHs and CV death. In well-treated populations of generally stable HFrEF participants in both the PARADIGM-HF and DAPA-HF studies, for example, there was ongoing residual risk in both treatment arms with incidence rates ranging from 10.5 to 15.3 participants with an event per 100 patient-years of follow-up for the composite of CV death or HFH, highlighting this unmet medical need [McMurray, J. J., et al 2014] [Srivastava, P. K., et al 2018] [McMurray, J. J. V., et al 2019].

The VICTORIA study demonstrated that vericiguat reduces the risk of CV death and HFH in a well-treated, but very high-risk population of adults with chronic HFrEF who have experienced a recent worsening HF event, specifically an HFH or need for IV diuretic therapy [Armstrong, P. W., et al 2020]. The benefit-risk of initiating vericiguat in a chronic HFrEF population (ie, patients without a recent worsening event and with lower NT-proBNP levels) remains is not known, although extrapolation from VICTORIA data suggests that this population may derive even greater benefit. Furthermore, vericiguat targets a critical molecular pathway in HF that is not addressed by other GDMT including beta-blockers, ACEIs, ARBs, MRAs, and an ARNI, or by SGLT2is.

2.2 Background

Refer to the IB/approved labeling for detailed background information on vericiguat.

2.2.1 Pharmaceutical and Therapeutic Background

Vericiguat is an sGC stimulator. HF is associated with impaired synthesis of NO and decreased activity of its receptor, sGC. Soluble guanylate cyclase catalyzes synthesis of intracellular cGMP, an important signaling molecule that regulates critical physiological processes such as cardiac contractility, vascular tone, and cardiac remodeling. Deficiency in sGC-derived cGMP contributes to myocardial and vascular dysfunction. Vericiguat restores the relative deficiency in this signaling pathway by directly stimulating sGC, independently of and synergistically with NO, to augment the levels of intracellular cGMP, which may improve both myocardial and vascular function. The complementary CV benefits of vericiguat in HF patients are therefore attributed to the active restoration of the deficient NO-sGC-cGMP pathway driving HF progression.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Chronic HF is a major source of morbidity and mortality. Clinical outcomes for patients with chronic HF remain poor, despite contemporary evidence-based therapies. Therefore, drugs are needed that effectively target disease mechanisms not addressed by current standard therapy. Vericiguat has a novel mode of action that targets endothelial dysfunction to improve regulation of vascular tone and myocardial function.

The results of the VICTORIA study showed a favorable benefit-risk profile for the use of vericiguat in patients with chronic HFrEF following a recent worsening event. Vericiguat has a clinically meaningful benefit on the endpoints of HFH and CV death. The AE profile in VICTORIA was predominantly associated with vericiguat's mechanism of action (eg, dyspepsia, nausea, headache) or similar to that reported with another sGC stimulator (anemia), and these events are generally nonserious and manageable even in this high-risk population. Slightly higher proportions of participants with anemia AEs were observed in the vericiguat group (9.6%) compared with the placebo group (7.4%). There was no increased risk of bleeding associated with vericiguat. The effect on BP during the study was small; there was an approximately 1 to 2 mm Hg greater mean reduction in SBP in participants who received vericiguat compared with placebo over the course of the study. The pharmacodynamic effects of vericiguat were evaluated after single and multiple-dose administrations in healthy participants and in participants with HF and are consistent with the predicted effects of an sGC stimulator on smooth muscle relaxation and vasodilation. Titrated up to a target dose of 10 mg vericiguat, the current risks are manageable. Vericiguat is a new therapeutic option to fulfill the unmet medical need in patients with chronic HFrEF.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In adults with chronic heart failure with reduced ejection fraction receiving guideline-directed medical therapy for heart failure:

Primary Objective	**Primary Endpoint**
Objective: To evaluate the efficacy of vericiguat compared with placebo on reducing the risk of cardiovascular death or heart failure hospitalization Hypothesis (H1): Vericiguat is superior to placebo in reducing the risk of cardiovascular death or heart failure hospitalization.	Time from randomization to the first event of cardiovascular death or heart failure hospitalization
Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate the efficacy of vericiguat compared with placebo on reducing the risk of cardiovascular death Hypothesis (H2): Vericiguat is superior to placebo in reducing the risk of cardiovascular death.	Time from randomization to cardiovascular death
Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the risk of heart failure hospitalization Hypothesis (H3): Vericiguat is superior to placebo in reducing the risk of the first event of heart failure hospitalization. Hypothesis (H4): Vericiguat is superior to placebo in reducing the risk of all heart failure hospitalization events.	-Time from randomization to the first event of heart failure hospitalization -Time from randomization to all heart failure hospitalization events

Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the risk of all-cause mortality or heart failure hospitalization Hypothesis (H5): Vericiguat is superior to placebo in reducing the risk of all-cause mortality or heart failure hospitalization.	Time from randomization to the first event of all-cause mortality or heart failure hospitalization
Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the risk of all-cause mortality Hypothesis (H6): Vericiguat is superior to placebo in reducing the risk of all-cause mortality.	Time from randomization to all-cause mortality
Objective: To evaluate the safety and tolerability of vericiguat compared with placebo	-Selected nonserious adverse events -Serious adverse events -Events of clinical interest
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the risk of heart failure hospitalization or urgent heart failure visit, defined as a heart failure visit that does not meet the criteria for heart failure hospitalization	Time from randomization to the first event of heart failure hospitalization or urgent heart failure visit
Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the risk of cardiovascular hospitalization	Time from randomization to the first event of cardiovascular hospitalization
Objective: To evaluate the efficacy of vericiguat compared with placebo in reducing the total number of heart failure hospitalization events	Total number of heart failure hospitalization events
Objective: To evaluate the efficacy of vericiguat compared with placebo on the health-related quality of life measures	-Change from baseline in EuroQol Five-Dimension Questionnaire measures -Change from baseline in Kansas City Cardiomyopathy Questionnaire measures

Objective: To evaluate the treatment effect of vericiguat compared with placebo on kidney function	Slope of change in eGFR from baseline
Objective: To evaluate the plasma pharmacokinetics of vericiguat	Plasma vericiguat concentration
Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study	Germline genetic variation and association to clinical data collected in this study
Objective: To evaluate the treatment effect of vericiguat compared with placebo on exploratory biomarkers	Change from baseline in exploratory biomarkers

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multisite, double-blind, event-driven, Phase 3 clinical outcome study of the sGC stimulator, vericiguat, in adults with chronic HFrEF. In this study, chronic HFrEF is defined as no HFH within 6 months or outpatient IV diuretic use within 3 months before randomization.

Approximately 6000 participants will be randomly allocated in a 1:1 ratio to either vericiguat or matching placebo on a background of GDMT. Enrollment of participants on ARNI and SGLT2i therapy is encouraged, with the goals of approximately 30% of the randomized population prescribed ARNI and, independently, 15% prescribed SGLT2i at baseline. The desired proportion of participants on GDMT may be achieved by capping the number of participants not on ARNI or SGLT2i therapy at randomization in IRT to avoid under-representation of these participant subgroups. Likewise, achieving the desired proportion of participants without previous HFH (approximately 30% to 40% of the study population) may require capping the number of participants with a history of HFH. Enrollment of participants with eGFR 15 to 30 mL/min/1.73 m^2 range will be limited to approximately 15% of the total study population. An important goal of the study will be to ensure adequate enrollment of participants historically underrepresented in HF studies.

Titration to the target dose of 10 mg once daily will be based on tolerability (see Section 6.6). The primary endpoint will be time to first event of CV death or HFH in participants with chronic HFrEF on GDMT. Participants will be treated until the Final Visit, which will be scheduled after required numbers of CV deaths (approximately 590) are observed. Based on an assumed placebo incidence rate of 6.0 participants with a CV death event per 100 patient-years of follow-up, the projected median follow-up will be 22.5 months. All participants will be followed until study completion to assess for the occurrence of endpoint events and for 14 days after last treatment dose for selective AE monitoring. Clinical outcome events will be adjudicated by an independent CEC. An external DMC will monitor data for safety. There will be a formal IA with the potential to stop the study for overwhelming evidence of efficacy as described in Section 9.7.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

Unlike VICTORIA, which enrolled a worsening chronic HFrEF population, the target population for this study is adults with chronic HFrEF. As such, only those participants who have not had a recent worsening event (including an HFH within 6 months or IV diuretic use without hospitalization within 3 months) will be included. Risks of recurrent HFH and of CV death decrease significantly within a few months of a worsening event and excluding those who have had an event in the preceding 6 months will ensure that the population enrolled does not overlap with that of VICTORIA. Another difference is an inclusion

criterion limiting enrollment to those who have an EF of 40% or less, consistent with the current HF guideline definition of HFrEF.

The lower limits of the screening NT-proBNP entry criterion match those used in both the PARADIGM-HF and DAPA-HF studies. This enrichment criterion is well-accepted in the HF literature and will ensure that enrolled participants have chronic HFrEF with residual risk for events.

NT-proBNP can be both a marker of disease severity and of ongoing decompensation. The upper limit of the screening NT-proBNP entry criterion of 6000 pg/mL will help minimize enrollment of those participants who have subclinical worsening of their HF. In VICTORIA, participants with baseline NT-proBNP levels less than 4000 pg/mL derived the greatest benefit from vericiguat with the benefit attenuating as baseline NT-proBNP levels approached 8000 pg/mL [Ezekowitz, J. A., et al 2020].

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the time to first event of CV death or HFH. This integrated measure of HF morbidity and mortality is a frequently used primary endpoint in Phase 3 HFrEF studies, including VICTORIA.

Secondary and Exploratory Efficacy Endpoints

The secondary efficacy endpoints include time to an event of CV death, time to the first event of HFH, time to all HFH events, time to the first event of all-cause mortality or HFH, and time to all-cause mortality. The exploratory endpoints include time to the first event of UHF visit or HFH, time to the first event of CV hospitalization, total number of HFH events, eGFR slope, and change from baseline in KCCQ, and EQ-5D-5L. These endpoints are additional measures of HF morbidity and mortality frequently evaluated in Phase 3 HFrEF studies.

4.2.1.2 Safety Endpoints

A selective approach to AE data collection will be utilized since the safety profile for vericiguat has been well characterized throughout the clinical program and will be further monitored in the postmarketing setting. This approach includes limited AE collection with selected NSAEs being reported by sites (Section 8.4). Additional country-specific requirements for adverse event reporting are described in Appendix 7. All SAEs and other reportable events will be collected as described in Section 8.4.1.

Other safety assessments will include physical examination findings, and vital signs including pulse rate and BP assessment. Laboratory safety studies will include blood chemistry, hematology, and pregnancy testing (performed in WOCBP).

Symptomatic hypotension, anemia, and laboratory values consistent with potential DILI events were selected as the prespecified ECIs for this study (Section 8.4.7). Symptomatic hypotension was selected based on vericiguat's mechanism of action. Anemia was selected based on an increased incidence of anemia noted in the VICTORIA study. Potential DILI events are captured per standard requirement of Sponsor studies.

4.2.1.3 Pharmacokinetic Endpoints

PK assessments obtained from the data collected during this study are exploratory and will be investigated under a separate detailed PK evaluation and analysis plan.

4.2.1.4 Planned Exploratory Biomarker Research

The exploratory biomarker analyses will provide insights into the potential mechanisms of therapeutic effect in HF beyond what is currently understood about how vericiguat affects cellular function.

4.2.1.4.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME, mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

Country-specific requirements are noted in Appendix 7.

4.2.1.5 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their

therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6. Country-specific requirements-are noted in Appendix 7.

4.2.2 Rationale for the Use of Comparator/Placebo

Vericiguat is being developed for use on a background of GDMT rather than as a replacement for any established therapy. To allow a blinded assessment, vericiguat will be compared with a matching placebo. While VICTORIA demonstrated a clinically meaningful benefit of vericiguat for the treatment of worsening chronic HFrEF on top of GDMT, chronic HFrEF patients were excluded from the study. As such, the benefit of vericiguat in chronic HFrEF patients on top of GDMT is unknown. Utilizing placebo as a comparator for vericiguat allows for a representative population receiving GDMT.

Participants who experience an HF event during the study should be encouraged to complete the study on their assigned blinded study intervention. In the cases where a participant's physician feels strongly that the participant should start open-label (commercially available) vericiguat, the blinded study intervention must be permanently discontinued for a minimum of 14 days to allow full safety monitoring of study intervention, followed by safe titration of open-label vericiguat as per the local prescribing guidelines (Section 7.1). Participants whose physicians initiate treatment with open-label vericiguat should continue in the study for follow-up, and vericiguat should be recorded as a concomitant medication (Section 6.5).

4.3 Justification for Dose

The starting dose for this study is 2.5 mg vericiguat or matching placebo, once daily. A titration regimen will be used to achieve the target dose of 10 mg vericiguat or matching placebo as described in Section 6.6.

4.3.1 Rationale for the Dose Selection/Regimen/Modification

The target dose and titration regimen for this study are based on data from the Phase 1 program in healthy volunteers, the Phase 2b study SOCRATES-REDUCED in HFrEF, and the Phase 3 VICTORIA study in HFrEF. In VICTORIA, this regimen was well tolerated with approximately 90% of participants receiving the target dose of 10 mg vericiguat once daily at 1 year.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of Final Contact with the last participant, whichever comes last.

For studies conducted in the European Economic Area (EEA), the local start of the study is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

Early study termination will be the result of the following specified criteria:

- A decision by the EOC to follow the unblinded external DMC's recommendation to stop the study due to either overwhelming evidence of efficacy at the IA, or if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is deemed unacceptable (Sections 9.7, 10.1.4.2, and 10.1.4.3).

In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

4.4.2 Primary Completion Date

A blinded Sponsor clinical team will monitor the accrual of CEC-confirmed primary composite endpoint and CV death events throughout the study. The Primary Completion Date will be defined when the target number of CV death events are expected to have occurred. The Primary Completion Date will be used for operational and statistical procedures. For participants receiving study intervention, sites will be instructed to perform a Final Visit after the Primary Completion Date. For participants who have prematurely discontinued study intervention, sites will be instructed to conduct a Final Contact after the Primary Completion Date. Events and measurements occurring up to and including the Primary Completion Date will be the basis of the primary study results.

5 STUDY POPULATION

Male or female participants with chronic HFrEF aged at least 18 years will be enrolled in this study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data is to follow all local laws and guidelines in keeping with the needs for participant confidentiality while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has a history of chronic HF (NYHA Class II to IV) on GDMT with no events of HFH within 6 months or outpatient IV diuretic use within 3 months before randomization.

Demographics

2. Is male or female, from 18 years of age, at the time of providing documented informed consent.

Female Participants

3. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 1 month after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

  - Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.

  - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

  - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

4. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

5. Has a screening NT-proBNP level within 30 days before randomization as shown in Table 1. For participants with multiple NT-proBNP results during screening, the most recent value will be used to determine eligibility at the Randomization Visit.

Table 1 NT-proBNP Inclusion Criteria

	NT-proBNP (pg/mL)
Sinus rhythm	600 to 6000
Atrial fibrillation	900 to 6000
NT-proBNP=N-terminal pro-brain natriuretic peptide. The most appropriate natriuretic peptide level cutoff should be guided by the participant's heart rhythm at the time of sample collection. Participants with paroxysmal atrial fibrillation with evidence of atrial fibrillation within 24 hours of sample collection will use the 900 pg/mL cutoff.	

6. Has an LVEF of ≤40% assessed within 12 months before randomization by any imaging method. The most recent measurement must be used to determine eligibility.

   NOTE: Participants who have undergone a coronary revascularization (PCI or CABG), valve repair/replacement, or implantation of CRT device or any other surgical, device, or pharmacological intervention (ie, initiation of a GDMT) that might improve LVEF, must have a measurement of LVEF at least 3 months after the intervention to be eligible.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has SBP <100 mm Hg or symptomatic hypotension.

2. Has a known allergy or sensitivity to vericiguat, any of its constituents, or any other sGC stimulator.

3. Is awaiting heart transplantation (United Network for Organ Sharing Class 1A / 1B or equivalent), is receiving continuous IV infusion of an inotrope, or has or anticipates receiving an implanted ventricular assist device.

4. Has amyloidosis or sarcoidosis.

Cardiac Comorbidity

5. Has primary valvular heart disease requiring surgical procedure or intervention or has undergone a valvular surgical procedure or intervention within 3 months before randomization.

6. Has hypertrophic cardiomyopathy.

7. Has acute myocarditis or Takotsubo cardiomyopathy.

8. Has received a heart transplant.

9. Has tachycardia-induced cardiomyopathy and/or uncontrolled tachyarrhythmia.

10. Has acute coronary syndrome (unstable angina, NSTEMI, or STEMI), undergone CABG or PCI within 3 months before randomization, or indication for coronary revascularization at the time of randomization.

11. Has symptomatic carotid stenosis, TIA, or stroke within 3 months before randomization.

12. Has a history of repaired or unrepaired simple congenital heart disease (eg, atrial or ventricular septal defects, or patent ductus arteriosus) with ongoing hemodynamically significant residual lesions, or any history of complex congenital heart disease (eg, tetralogy of Fallot, transposition of the great arteries, single ventricle disease) regardless of repair status.

13. Has active endocarditis or constrictive pericarditis.

Noncardiac Comorbidity

14. Has an eGFR based on the CKD-EPI Creatinine Equation of <15 mL/min/1.73 m^2 within 30 days before randomization or is on chronic dialysis. For participants with multiple eGFR results during screening, the most recent value will be used to determine eligibility at the Randomization Visit.

15. Has severe hepatic insufficiency defined as ALBI Grade 3 or hepatic encephalopathy, or has hepatic laboratory abnormalities (ALT or AST ≥3 × ULN or total bilirubin ≥2 × ULN). Screening albumin, ALT, AST, and total bilirubin results within 30 days before randomization may be used for assessment of laboratory abnormalities or the calculation of the ALBI score. For participants with multiple albumin and/or total bilirubin results during screening, the most recent value for each test will be used to calculate ALBI score as defined in Appendix 8 [Fragaki, M., et al 2019].

16. Has malignancy or other noncardiac condition limiting life expectancy to <3 years.

17. Requires continuous home oxygen for severe pulmonary disease.

18. Has interstitial lung disease.

Prior/Concomitant Therapy

19. Had any discontinuation or dose modification of GDMT (including beta blockers, ACEI/ARBs, ARNI, MRAs, hydralazine-nitrate combinations, SGLT2is, or ivabradine) or vericiguat within 4 weeks before randomization.

20. Has concurrent or anticipated concomitant use of PDE5 inhibitors such as vardenafil, tadalafil, and sildenafil during the study.

21. Has concurrent use of an sGC stimulator such as riociguat or vericiguat.

Prior/Concurrent Clinical Study Experience

22. Has participated in another interventional clinical study or has been treated with another investigational product ≤30 days before randomization or plans to participate in any other study or study intervention during this study.

Diagnostic Assessments

Not applicable.

Other Exclusions

23. Has a recent history (within the last year) of drug or alcohol abuse or dependence.

24. Is pregnant or breastfeeding or plans to become pregnant or to breastfeed during the study.

25. Has a medical disorder, condition, or history thereof that in the opinion of the investigator would impair the participant's ability to participate in or complete the study.

26. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a diet consistent with recommendations in local guidelines, such as the ACCF/AHA and ESC Guidelines for the Management of Heart Failure during the study [Ponikowski, P., et al 2016] [Yancy, C. W., et al 2017].

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (study intervention(s) provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Vericiguat	Experimental	MK-1242 (vericiguat)	Drug	Tablet	2.5 mg, 5 mg, and 10 mg	2.5 mg, 5 mg, or 10 mg QD	Oral	Titration: 2.5 mg titrated to 5 mg titrated to 10 mg / Day 1 until end of treatment	Test Product	IMP	Provided centrally by the Sponsor
Placebo	Placebo Comparator	Placebo for MK-1242 (vericiguat)	Drug	Tablet	0 mg matching placebo for 2.5 mg, 5 mg, and 10 mg	0 mg QD	Oral	Sham Titration: 0 mg / Day 1 until end of treatment	Placebo	IMP	Provided centrally by the Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

For detailed instruction for dose titration and modification see Section 6.6.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.9 for details regarding administration of the study intervention.

All placebos were created by the Sponsor to match the active product.

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific evaluations required to select the proper dose for each participant are outlined in Section 6.6. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to vericiguat or matching placebo, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to baseline NYHA Class (II vs III/IV).

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-1242 (vericiguat) and placebo will be packaged identically so that blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment with compliance <80% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Sponsor consultation and written documentation on participant management is not required if the reason for <80% compliance is due to protocol-specified interruptions per the dose modification scheme (Section 6.6), investigator discretion, and/or an AE. Such instances of <80% compliance, as well as any instance of compliance between 80% and 100%, will not be considered a protocol deviation.

Administration of the first dose of study intervention will be witnessed by the investigator or designee at the Randomization Visit only (Visit 2).

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

- Compliance with self-administered study intervention will be assessed at each scheduled visit. Assessments will be based on counting of returned tablets corroborated with participant reporting. To facilitate this, participants must be instructed to return all of the study intervention packaging including unused study intervention and empty packaging.

- Any discrepancies between actual and expected amount of returned study intervention must be discussed with the participant at the time of the visit, and any explanation must be documented in the source records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will be recorded in the eCRF.

6.5 Concomitant Therapy

Per protocol, all participants should receive GDMT based on locally relevant guidelines such as ACCF/AHA and ESC Guidelines for the Management of Heart Failure applied individually at the discretion of the treating investigator and in line with individual tolerability [Ponikowski, P., et al 2016] [Yancy, C. W., et al 2017]. This includes medications such as beta blockers, ACEIs, ARBs, ARNI, MRAs, hydralazine-nitrate combinations, SGLT2is, ivabradine, and cardiac device therapies such as ICDs and biventricular pacemakers. Use of treatment expected to be reflected in future recommendations should be considered. Use of short and long-acting nitrates is permitted.

Medications specifically prohibited in the exclusion criteria are not allowed for concomitant use with study intervention. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any medical therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Participants whose physicians initiate treatment with open-label vericiguat should continue in the study for follow-up (Section 4.2.2, Section 7.1), and vericiguat should be recorded as a concomitant medication.

Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines.

As described in the DEGs, investigators should record the following:

- Medications taken within 30 days before and on the date of randomization.
- Medications taken to treat HF (GDMT and any diuretics) during the period beginning 30 days before enrollment (Visit 1) through 14 days after the last dose of study intervention (14-day Safety Contact).
- Medications administered within 14 days before and during a clinical endpoint event, SAE, ECI, and other reportable events until recovery/stabilization of event.
- All licensed COVID-19 vaccines received during the period beginning 30 days before enrollment (Visit 1) through 14 days after the last dose of study intervention (14 day Safety Contact).

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Titration)

Participants will start with a 2.5 mg oral dose of blinded vericiguat or matching placebo once daily. The first titration to 5 mg vericiguat or matching placebo daily will occur at Visit 3 (14±4 days after randomization). The second titration to the target dose of 10 mg vericiguat or matching placebo daily will occur at Visit 4 (28±4 days after randomization). These titration steps include sham titrations in the placebo arm. Dose titration will depend on mean sitting SBP and symptoms indicative of hypotension before administration of the dose as described in Table 3.

If the participant does not reach the 10-mg dose by 28±4 days after randomization, up-titration will be encouraged at any subsequent visit at the discretion of the investigator according to the SBP criteria in Table 3.

The intention of the protocol is to maintain participants on the 10-mg target dose of study intervention for as long as possible after randomization. However, if in the opinion of the investigator the participant does not tolerate the 10-mg target dose, in addition to considering reduction of the study intervention dose, the investigator should consider whether medications not shown to provide a HF benefit in clinical studies (eg, various classes and doses of calcium channel blockers or alpha-blockers) can be reduced before reducing the dose of the study intervention. For example, in the case of symptoms of orthostatic hypotension, the investigator should also consider the volume status and whether there is a necessity to change the dose of diuretics or alpha-blockers. If such adjustment or discontinuation of concomitant medications that are not associated with an outcome benefit is not possible or does not resolve signs and symptoms of intolerability, the investigator may at any time during the course of the study reduce the dose or interrupt study treatment in participants who no longer tolerate the current study intervention dose. The doses of disease modifying drugs shown to provide an outcome benefit, such as beta blockers, ACEI/ARBs, ARNI, MRAs, hydralazine-nitrate combinations, SGLT2is, or future standard treatment recommended in the study population, should not be reduced for the sole purpose of facilitating the maintenance of study intervention dosing. In general, every attempt should be made to resume the study intervention upon temporary interruption and reach and maintain the 10-mg target dose of the study intervention when the investigator feels it is medically appropriate according to Table 3 and Table 4.

Table 3 Systolic Blood Pressure Criteria for Study Intervention Dose Modification

Blood Pressure Assessment	**Dose Modification**
SBP ≥100 mm Hg and not on 10-mg target dose	Increase Dose
• SBP ≥100 mm Hg and on 10-mg target dose OR • SBP ≥90 and <100 mm Hg	Maintain Dose
SBP <90 mm Hg, asymptomatic	• If currently on 5 or 10 mg, decrease dose • If currently on 2.5 mg, interrupt dose
SBP <90 mm Hg, symptomatic	Interrupt Dose

A dose decrease from the 5- or 10-mg doses is possible at any time if the investigator feels this is justified for safety reasons.

A dose assessment including reasons for dose modifications (maintenance, increase, decrease, interruption, or restart) will be collected at all visits in which a vital signs assessment is performed. Study intervention initiation, up-titration, or restart should only occur if mean SBP is ≥100 mmHg.

If the participant is not receiving the target dose of 10 mg, up-titration should be considered at any study visit at the discretion of the investigator according to the SBP criteria in Table 3.

Unscheduled visits may be used at the discretion of the investigator for up-titration and resumption of study intervention following interruptions (Section 8.11.2.2). Study intervention should be resumed as soon as medically justified at the discretion of the investigator.

There is no defined maximum time limit for temporary treatment interruption. In all cases, the reason for study intervention interruption or permanent study intervention discontinuation must be recorded in the eCRF.

6.6.1 Resumption of Study Intervention Following Interruption

Titration rules following restart of study intervention after temporary interruption due to intolerability are as follows:

- Interruption during the titration phase (Days 0 to 28):
  - Restart study intervention at a scheduled visit and titrate with intervals as shown in Table 3 and Table 4.

- Interruption After Day 28
  - Restart as soon as possible (with an unscheduled visit if required) and titrate according to the instructions provided in Table 3 and Table 4.
  - Participant will then resume the planned visit schedule.
  - Unscheduled visits and/or contacts can be conducted at the discretion of the investigator (Section 8.11.2.2).

Table 4 Instructions for Resumption of Study Intervention After Interruption due to Intolerability

Dose at Time of Interruption	Length of Interruption	Restart Dose	Dose Level 1st Titration (14 days ± 4)	Dose Level 2nd Titration (28 days ± 4)
2.5 mg	Any time interval	2.5 mg	5 mg	10 mg
5 mg	Any time interval	2.5 mg	5 mg	10 mg
10 mg	>5 days	2.5 mg	5 mg	10 mg
10 mg	≤5 days	5 mg	10 mg	Not applicable

In cases when study intervention was interrupted for reasons other than intolerability, the investigator may use clinical judgment in restarting study intervention based on considerations including participant's prior history of tolerability to the intervention. Table 4 may be used at the discretion of the investigator as a guide for resumption of study intervention in such situations.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.12). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

Since data on clinical events and vital status are essential to the primary analysis, they must be collected until the end of the study, even if the participant prematurely discontinues study intervention. Therefore, all efforts will be taken to obtain data on clinical events and vital status until the end of study. All participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits/contacts and procedures as specified in Section 1.3.2 and Section 8.11.3 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- If the participant begins treatment with open-label vericiguat (see Sec. 6.5).
- Participant has an eGFR that is consistently <15/mL/min/1.73 m^2 or requires chronic dialysis.

  Note: Vericiguat has not been studied in patients with eGFR <15 mL/min/1.73 m^2 at treatment initiation or on dialysis and is therefore not recommended in these patients. If short-term dialysis is indicated, then interrupt study intervention prior to the start of dialysis and resume only after stopping dialysis and when the eGFR returns to ≥15 mL/min/1.73 m^2.
- The participant has a confirmed positive serum pregnancy test.

Participants may be allowed to begin study intervention again if deemed medically appropriate, after consultation with the Sponsor.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant or a participant's legally acceptable representative requests to withdraw consent from the study, the investigator will clarify whether the participant wishes to withdraw completely from study (eg, no further site contact) or whether the participant is willing to be contacted for additional follow-up by phone. If the participant is willing to be contacted about their health status at a future timepoint, then the participant is not withdrawn from study follow-up. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.11. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

For participants who have withdrawn consent from further study follow-up, collection of clinical event and vital status data will be completed by review of medical or public records in accordance with participant informed consent and local regulations.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.
- At any time that a participant's vital status is in question, the investigator should explore all possible options to locate the participant per local regulations (unless the participant has explicitly withdrawn his/her consent to any type of follow-up). The site must document all attempts to try to contact the participant in the medical records/source documents. The vital status will be collected for all randomized participants who have not withdrawn consent, irrespective of completion of study procedures.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The estimated amount of blood collected from each participant over the duration of the study will be 116 mL (Laboratory Manual). This estimate is based on the median follow-up of 22.5 months. The actual blood volume could be less or more depending on when the participant is enrolled relative to the Primary Completion Date. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 LVEF Assessment

A historical assessment of LVEF within 12 months before randomization may be used for screening. The most recent results must be used to determine eligibility. For participants without a historical LVEF assessment, an echocardiogram will be performed at screening to determine eligibility.

NOTE: Participants who have undergone a coronary revascularization (PCI or CABG), valve repair/replacement, or implantation of CRT device or any other surgical, device, or pharmacological intervention (ie, initiation of a GDMT) that might improve LVEF, must have a measurement of LVEF at least 3 months after the intervention to be eligible.

8.1.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.4 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.5 Medical History

A medical history will be obtained by the investigator or qualified designee at the Screening Visit; participant demographics will also be recorded. At the Randomization Visit, the medical history record will be updated with any new diagnoses that have occurred during the screening period.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 30 days before starting the study.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record all medications taken by the participant during the study as described in Section 6.5. The investigator or qualified designee will confirm that the participant is not receiving any medications prohibited during the study as described in Section 5.2.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Each participant may only be rescreened once. Any participant who is rescreened will retain the original screening number assigned at the initial Screening Visit. Specific details on the Screening/Rescreening Visit requirements are in Section 8.11.1.2.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.9 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Operations Manual.

The first dose of study intervention will be administered at the study site at Visit 2 only. Subsequent dosing will be performed once daily by the participant (ie, unsupervised at his/her home) at approximately the same time each day.

The procedures for vital sign measurements required before and after the first dose of study intervention at Visit 2 are described in Section 8.3.2. At subsequent visits, perform vital sign measurements and dose assessment and modification (Sections 8.3.2 and 8.3.3) before dispensing study intervention.

8.1.9.1 Timing of Dose Administration

Study intervention should be taken with food at the same time each day. If a dose is missed, it should be taken as soon as the participant remembers on the same day of the missed dose. Participants should not take 2 doses of study intervention on the same day.

8.1.10 Study Intervention Compliance

Refer to Section 6.4 for instructions for recording study intervention compliance.

8.1.11 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 1.3.2) and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Study Intervention Discontinuation Visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Sections 8.4 and 8.11.3.

8.1.11.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.12 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

8.1.13 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Clinical Events Assessment

Participants will be assessed for the occurrence of potential study endpoint events described in Section 9.4.1. Assessment for endpoint events will occur at each study visit as outlined in Section 1.3. The Sponsor may request this assessment at any time during the study in preparation for an IA. Investigators will also assess potential study endpoints they learn of between scheduled study visits.

8.2.2 New York Heart Association Functional Classification of Heart Failure

NYHA class will be assessed according to the classification in Table 5.

Table 5 New York Heart Association Functional Classification

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity in which ordinary physical activity leads to fatigue, palpitation, dyspnea, or anginal pain. The person is comfortable at rest.
III	Marked limitation of physical activity in which less-than-ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain. The person is comfortable at rest.
IV	Inability to carry on any physical activity without discomfort but also symptoms of heart failure or the anginal syndrome even at rest, with increased discomfort if any physical activity is undertaken

8.2.3 EuroQol Group 5-Dimension, 5-level Questionnaire

The EQ-5D is a questionnaire used to assess current health status as reported by patients, consisting of 5 domain questions and 1 VAS response. The domain questions assess mobility, self-care, usual activities, pain/discomfort, anxiety/depression, with 5-level response options: no problems, slight problems, moderate problems, severe problems, and

extreme problems. Summary scores will be calculated from the 5 domain scores according to scoring instructions from the EuroQol group and the EQ-5D-5L value sets for the United States and for Europe.

The EQ-5D VAS records patient self-rated health on a 20 cm vertical VAS with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine' and is scored on a 0 to 100 scale.

The questionnaire is available in over 60 translations with established validity, reliability, and responsiveness. In cases when a validated translation is needed and not available for a specific language, participants who speak that language will be exempt from the requirement to complete the questionnaire.

8.2.4 Kansas City Cardiomyopathy Questionnaire

The KCCQ questionnaire used in this study consists of a 23-item, self-administered questionnaire intended for the quantification of HF patients' perspectives of how their disease impacts their lives. The questionnaire requires, on average, 5 to 8 minutes for completion. The KCCQ measures the impact of patients' HF, or its treatment, on 7 distinct domains using a 2-week recall period: symptom frequency, symptom burden, physical limitation, health perceptions, social function, self-efficacy, and symptom stability. The KCCQ domains of self-efficacy and symptom stability will be reported but are not considered in the efficacy assessment as they address patient knowledge and recent changes in symptoms respectively.

In addition, there are 3 summary scores; a total symptom scale that combines the symptom frequency and the symptom burden scores, a clinical summary scale that combines the total frequency and physical limitation scores to replicate the NYHA Classification, and an overall summary score that includes the Total Symptom, Physical Limitation, Social Limitation, and QoL scores.

The questionnaire is available in over 40 translations with established validity, reliability, and responsiveness. In cases when a validated translation is needed and not available for a specific language, participants who speak that language will be exempt from the requirement to complete the questionnaire.

8.2.5 Vital Status Assessment

The vital status assessment is included in the Final Contact and may be conducted at any time during the study. This assessment can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations, unless the participant has specifically withdrawn consent for collection of vital status data.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes

drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A full physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard as outlined in the SoA. Height will also be measured once and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard as outlined in the SoA.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

BP and pulse rate (each measured in triplicate) and weight will be assessed at the Screening Visit, Discontinuation Visit, Final Visit and at each study visit before study intervention is dispensed. At the Randomization Visit (Visit 2), BP and pulse assessments will also be completed 2 ± 0.5 hours after study intervention administration.

Accurate measurement of BP is essential to guide dose titration management and to detect potential safety signals during the study. Several factors related to the participant can cause significant deviations in measured BP. These include room temperature, exercise, alcohol or nicotine consumption, positioning of the arm, muscle tension, bladder distension, talking, and background noise.

- No other procedures may be performed during the BP and pulse rate measurements.

- The participant should be asked to remove all clothing that covers the location of cuff placement.

- BP and pulse rate measurements should be preceded by at least 10 minutes of rest with the participant comfortably seated in a chair with the legs uncrossed and the back and arm supported in a quiet setting without distractions. Measurements should not be made while the participant is on an examining table. The participant should be instructed to relax as much as possible and to not talk during the measurement procedure.

- BP and pulse rate measurements will be assessed with the participant in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available. Whenever possible, BP measurements should be obtained using the same arm, same BP monitoring device, and same examiner at each visit.

- The examiner should ensure that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum).

- 3 consecutive BP measurements will be recorded at intervals of approximately 2 minutes apart. Record the time, positioning, and arm used for each measurement.

- Assessment of pulse rate can be manual (rather than using an automated device). When performed manually, pulse rate must be measured in the brachial/radial artery for at least 30 seconds.

- Body weight will also be measured and recorded.

Dose assessment should be performed following BP assessment (Section 8.3.3).

8.3.3 Dose Assessment and Modification

After BP assessment, perform a dose assessment using Table 3. If indicated, see Section 6.6 for instructions for dose modification.

8.3.4 Electrocardiograms

- Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

- Participants will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the procedure.

- 12-lead ECGs should be performed after the participant has rested quietly for approximately 10 minutes.

Record ECG with a paper speed of 25 mm/sec. Ensure standard calibration is performed and provide record of a calibration mark indicating the equivalence of 1 mV signal to 10 mm vertical deflection on the ECG.

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6 Pregnancy Testing

- Pregnancy testing:
    - Pregnancy testing requirements for study inclusion are described in Section 5.1.
    - Pregnancy testing (urine and/or serum as required by local regulations) should be conducted at monthly intervals during intervention. Sites will provide urine pregnancy testing kits to WOCBP for at-home testing every 4 weeks between visits. At scheduled study visits, site personnel will confirm with WOCBP that the required at-home pregnancy tests have been completed and will document such completion in site source records.
    - Pregnancy testing (urine and/or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for participant contraception in Section 5.1. The final pregnancy test is required 1 month after the last dose of study intervention and must be recorded in the site source records.
    - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

NOTE: If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. Participants should be instructed to contact the site if the result of a home pregnancy test kit cannot be confirmed as negative.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

Selective AE reporting by sites will be used in the study. The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

All events will be reported to the site by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of a selected NSAE, SAE, as well as other reportable safety events. Selected NSAEs are nonserious AEs that meet any of the following criteria:

- AE that leads to study intervention dose modification or discontinuation
- AE that leads to withdrawal from the study
- COVID-19 disease-related AE

Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up selected NSAEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of a selected NSAE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

Additional country-specific requirements for adverse event reporting are described in Appendix 7.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

Selected NSAEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention randomization through 14 days after cessation of study intervention, selected NSAEs, SAEs, and other reportable safety events must be reported by

the investigator. All pregnancy and exposure during breastfeeding, from the time of intervention allocation/randomization through 1 month post cessation of study intervention must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

Selected NSAEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 6.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Additional country-specific requirements for adverse event reporting are described in Appendix 7.

Table 6 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Target Consent to Main Consent Main Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
Selected NSAE **Additional country-specific requirements for adverse event reporting are described in Appendix 7.**	Report if: – due to protocol-specified intervention – causes exclusion	Report if: - leads to study intervention dose modification or discontinuation - leads to withdrawal from the study - COVID-19 disease-related **Additional country-specific requirements for adverse event reporting are described in Appendix 7.**	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event[a]
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event

Type of Event	Reporting Time Period: Target Consent to Main Consent Main Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation Through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
ECI (do not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – symptomatic hypotension - anemia	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Not required	Report all	Not required	Within 5 calendar days of learning of event (unless serious)

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

[a] Event meeting serious criteria and determined not to meet endpoint criteria (as per Section 8.4.6) must be reported within 1 business day from the time of receipt of the Sponsor query.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Selected NSAEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow selected nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

Additional country-specific requirements for adverse event reporting are described in Appendix 7.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Potential prespecified efficacy endpoints will be submitted to an independent CEC (See Section 10.1.4.4) for adjudication. This will include all-cause mortality, including CV death and non-CV death.

The following events will not be subject to expedited reporting by the Sponsor to investigators, IECs/IRBs, and regulatory agencies, regardless of causality unless and until the event is reviewed by the CEC and found not to meet the specified criteria in the CEC charter for the following endpoint types:

- CV death
- CV hospitalizations
- UHF visit

Fatal events that are adjudicated to be non-CV deaths by the CEC will require an independent MSD company causality assessment and will be subject to expedited reporting, where required by local legislation, when there is sufficient evidence suggesting a causal relationship between study intervention and the event.

If any event submitted for adjudication is determined by the CEC not to meet the endpoint criteria in the CEC charter, the event will then be subject to expedited reporting (as appropriate, based upon both the investigator and independent MSD company causality assessment of drug relationship, as required by local legislation).

All of the endpoint events including confirmed adjudicated CV events will be reviewed and monitored by an external DMC, unblinded to study intervention, as part of the overall assessment of safety and efficacy of vericiguat. Based upon the regular DMC review of unblinded safety results, the DMC is empowered by the DMC charter to make recommendations with regard to study conduct to assure the continuing appropriate safety of the participants.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as: an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).
2. Symptomatic hypotension
3. Anemia

ECIs of symptomatic hypotension and anemia that do not fit the SAE criteria do not require regulatory reporting Table 6.

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than 10 mg vericiguat QD.

Limited data are available with regard to overdosage in human patients treated with vericiguat. In the event of an overdose, hypotension may result. Symptomatic treatment

should be provided. Vericiguat is unlikely to be removed by hemodialysis because of high protein binding.

Decisions regarding dose interruptions or modifications following a suspected overdose will be made by the investigator in consultation with the Sponsor's Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

The decision as to which plasma samples collected will be measured for evaluation of PK will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be measured if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma MK-1242

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Laboratory Manual. Blood samples will be collected for PK analysis as indicated in the SoA. At Visit 2, 1 sample will be collected predose. For all PK samples, date and time of the PK sample collection and date and time of last dose of study intervention intake must be documented.

Additional blood samples for PK should be collected at Visit 4, Visit 5, and approximately every 48 weeks at routine visits. PK samples obtained at additional time points based on the investigator's discretion will not qualify as a protocol deviation and will be analyzed. Deviations from the specified time points will be documented and taken into account when calculating the PK parameters.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for genetic analysis
- Blood for exploratory biomarker analysis

Country-specific requirements are noted in Appendix 7.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.8.2 Exploratory Biomarker Sample Collection

In the event that the biomarker sample at the specified visit is not obtained, the sample can be taken at a subsequent visit within the next 12 months of treatment. Details on the collection, processing, storage, and shipment of biomarker samples will be provided in a separate Operations/Laboratory Manual and results of the biomarker analyses will be reported separately.

Investigators will not receive the results of analyses during the study, and no alerts will be sent.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research
- Leftover exploratory biomarker samples for future research

Country-specific requirements are noted in Appendix 7.

8.10 Health Economics, Medical Resource Utilization and Health Economics

Not applicable.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening Period

8.11.1.1 Target Screening (Optional)

A single, optional Target Screening Visit may be performed to assess potential eligibility for participants who do not have a recent (within 30 days) historical assessment of any of the protocol-specified laboratory screening tests. After providing documented informed consent for this optional Target Screening, participants will be assigned a screening number and undergo a blood draw. If the decision to proceed to study screening is made, documented consent for the full study will be obtained and the Screening Visit will be conducted.

8.11.1.2 Screening Visit

Up to 30 days before intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. For potential participants who are screen failures, 1 rescreening is allowed, which must include re-consenting potential participants.

The Screening Visit (Visit 1) and Randomization Visit (Visit 2) may occur on the same day if all required test results for the eligibility criteria are available.

8.11.2 Treatment Period

Clinic visits must be conducted at the study site. If there are extenuating circumstances that do not support an in-clinic visit (ie, incapacitating health conditions or local or national emergency situations), a telephone, video, or home visit using site staff or a nursing service may be used, if allowed by local regulations following consultation with the Sponsor.

8.11.2.1 Randomization Visit

The Randomization Visit (Visit 2) may occur on the same day as Screening Visit (Visit 1) if all required test results for the eligibility criteria are available. If Visits 1 and 2 occur on the same day, all procedures specified for both Visits 1 and 2 must only be conducted once after the participant has provided documented informed consent.

8.11.2.2 Unscheduled Visits

Unscheduled visits may be utilized at any time during the study at the discretion of the investigator. At unscheduled visits, the following assessments will be performed:

- AE review and reporting (see Section 8.4 and Appendix 3)
- BP and pulse rate (see Section 8.3.2) and dose assessment (see Section 8.3.3) before study intervention administration/dispensing
- Clinical event assessment (see Section 8.2.1)
- Concomitant medication review (see Sections 8.1.6.2 and 6.5)

Upon interruption of the study intervention due to intolerability, intake should be resumed as soon as medically justified at the discretion of the investigator as described in Section 6.6. Investigators should make every attempt to resume study intervention in all participants after interruption as soon as medically justified.

8.11.3 Participants Who Prematurely Discontinue Study Intervention

Participants who prematurely discontinue study intervention will have a Study Intervention Discontinuation Visit at the time of permanent discontinuation of study intervention and will continue to be monitored until the end of the study (Section 1.3.2). After the last dose of Study Intervention, participants will have a safety follow-up contact (see Section 8.11.4). After the safety contact, additional follow-up contacts will occur every 24 weeks (±14 days) relative to Randomization (Day 1), for clinical event assessment to monitor for efficacy endpoint events and vital status through the end of the study (Final Contact). Follow-up contacts may be conducted via telehealth visits, phone calls, etc.

8.11.4 14-day Safety Contact

All participants will be required to complete a safety follow-up contact at least 14 days after the last dose of study intervention to determine if any AEs have occurred since the Final Visit or Study Intervention Discontinuation Visit, as applicable.

8.11.5 Primary Completion Date Requirements

8.11.5.1 Final Visit

After the Primary Completion Date, a Final Visit will be conducted for participants who are receiving study intervention. Participants will continue study intervention until this visit and will be asked to stop taking study intervention at this visit.

8.11.5.2 Final Contact

After the Primary Completion Date, the Final Contact will be conducted for participants who prematurely discontinue study intervention. A Final Contact may be conducted via telehealth visit, phone call, etc.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data, exploratory biomarkers, PGA, FBR) are beyond the scope of this document or will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Pivotal Phase 3 Randomized Placebo-controlled Clinical Study to Evaluate Efficacy and Safety of the sGC Stimulator Vericiguat/ MK-1242 in Adults With Chronic Heart Failure With Reduced Ejection Fraction
Treatment Assignment	Participants will be assigned randomly in a 1:1 ratio to vericiguat or matching placebo, respectively. Stratification method: Treatment randomization will be stratified according to baseline NYHA Class (II vs III/IV).
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoint(s)	Time from randomization to the first event of CV death or HFH
Secondary Endpoints	Time from randomization to CV death Time from randomization to first event of HFH Time from randomization to all HFH events (first and recurrent) Time from randomization to the first event of all-cause mortality or HFH Time from randomization to all-cause mortality

Statistical Methods for Key Efficacy	The analysis of the primary endpoint will be performed with a one-sided stratified log-rank test to test whether the time to first event of CV death or HFH is prolonged in the vericiguat treatment group compared with placebo. The same approach will be used for the endpoints of time to CV death, time to first event of HFH, time to all-cause mortality, and time to the first event of all-cause mortality or HFH. The time to total HFH events will be tested with an Andersen-Gill model. The type I error rate will be controlled at 0.025 (one-sided).
Statistical Methods for Key Safety Analyses	95% CIs will be provided for between-treatment differences in the percentage of participants with selected events; these analyses will be performed using the Miettinen and Nurminen method.
Interim Analyses	One IA for efficacy is planned at the time when approximately 70% (413) of the planned number of CV deaths (approximately 590) are observed. An external DMC will assess the unblinded results of the IA and may recommend early study termination for success if both the primary endpoint and the CV death endpoint are statistically significant based on the nominal significance level used for the IA.
Multiplicity	Hypotheses H2 and H3 (addressing CV death and HFH), will both be tested if the test of H1 is significant. Hypotheses H4, H5, and H6 (addressing total HFH events, the composite of all-cause mortality or HFH, and all-cause mortality), will also be tested if the test of H1 is significant, and will follow a hierarchical testing approach. In addition, a multiplicity adjustment for the IA will be applied for the primary and secondary endpoints.
Sample Size and Power	The sample size calculation is driven by the CV death endpoint. The relative reduction in the hazard with vericiguat is assumed to be 20% for the CV death and primary endpoint, corresponding to a HR of 0.8. Using the log-rank test, approximately 590 CV deaths will be required to achieve 80% power conditional on a positive primary endpoint result with a one-sided alpha of 0.025. A sample size of 6000 participants is expected to produce 590 CV death events in approximately 39.5 months assuming a placebo incidence rate of 6.0 per 100 patient-years of follow up. It is expected that approximately 1080 participants will have experienced a primary event at the time of 590 CV death events assuming a placebo incidence rate of 11.5 participants with an event per 100 patient-years of follow up and a HR of 0.8. This number of participants with primary events (1080) will provide approximately 95% power for primary hypothesis testing. However, since the study duration will be driven by the number of CV death events, the number of primary endpoint events (and thus, the power) may differ from the numbers provided above.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house treatment blinding procedures. The laboratory values for NT-proBNP will also be blinded after randomization (Visit 2). The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an IVRS.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3 Hypotheses, Objectives, and Endpoints.

9.3.1 Estimands

The following attributes define the primary estimand addressing the primary hypothesis:

- The treatment condition of interest is vericiguat or placebo added to GDMT.
- The population targeted by the clinical question are males or females at least 18 years of age with chronic HFrEF (as defined in Section 5).
- The endpoint to address the clinical question is time to the composite endpoint of CV death or HFH, defined as the time from the date of randomization to the date of first occurrence of any endpoint event.
- Intercurrent events of interest are discontinuation of study intervention and loss to follow-up (ie, withdrawal of consent, non-CV death). A treatment policy approach will be applied to discontinuation of study intervention, and a hypothetical strategy will be applied to lost to follow-up (ie, as though participants would have been followed for the primary endpoint events).
- The population-level summary is the hazard ratio comparing vericiguat with placebo.

Analogous estimands will be used to evaluate the secondary objectives and hypotheses, except that the population-level summary for H4 (related to all occurrences of HFHs) will be the ratio of incidence rates rather than the hazard ratio.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary Endpoint

- Time from randomization to the first event of CV death or HFH

Secondary Endpoints

- Time from randomization to CV death
- Time from randomization to first event of HFH
- Time from randomization to total HFH events (first and recurrent)
- Time from randomization to first event of all-cause mortality or HFH
- Time from randomization to all-cause mortality

Exploratory Endpoints

- Time from randomization to first event of HFH or UHF visit (not meeting the criteria for an HFH)
- Time from randomization to first event of CV hospitalization
- Total number of HFH events
- Change from baseline in health-related quality of life measures (EQ-5D-5L and KCCQ)
- Slope of change in eGFR from baseline

All of the above endpoints except change in eGFR and quality of life measures will be based on CEC-confirmed events.

9.4.2 Safety Endpoints

Safety measurements are described in Section 8 Study Assessments and Procedures.

9.5 Analysis Populations

The primary efficacy analysis population will be the ITT population, comprised of all randomized participants. Participants without any post-randomization information will be censored at Day 1.

Except where noted otherwise, all efficacy analyses will classify participants according to their randomized intervention.

The population for all safety analyses will be the APaT population, comprised of all randomized participants, who have taken at least 1 dose of study intervention (vericiguat or placebo). All participants will be analyzed according to the actual intervention received. Any participants who inadvertently received both study interventions (placebo and blinded vericiguat) during the study will be analyzed according to the planned intervention.

9.6 Statistical Methods

9.6.1 Efficacy Analyses

Analysis of Primary Endpoint

The analysis of the primary endpoint will test whether the time to the first event of the composite endpoint is prolonged in the vericiguat intervention group compared with placebo. Randomized participants without any HFH or CV death events at the time of analysis will be censored at the earliest of: their last available information, the Primary Completion Date when the planned number of CV death events is achieved (Section 4.4.2), or the date of their non-CV death.

The analysis will be performed with a one-sided stratified log-rank test using the same stratification factor for randomization with a one-sided type I error rate of 0.025 (Table 7).

Kaplan-Meier estimates of the primary composite endpoint survival curves and the corresponding 95% CIs will be presented for each intervention group. The hazard ratio and corresponding 95% CI will be estimated based on a Cox proportional hazards model stratified by the stratification factor for randomization.

In addition, as a sensitivity analysis the primary endpoint will be analyzed using the 5-STAR stratified testing approach by Mehrotra and West [Mehrotra, D. V. 2020].

The number and proportion of participants with a primary endpoint event, as well as incidence rates per 100 patient-years of follow-up, will be provided by intervention group.

Analysis of Secondary Endpoints

A one-sided stratified log-rank test similar to the one used for the primary efficacy endpoint will also be used to test whether the time to first HFH, time to CV death, time to all-cause mortality, and time to first event of all-cause mortality or HFH is prolonged in the vericiguat intervention group compared with placebo. Randomized participants without any endpoint events at the time of analysis will be censored at the earliest of: their last available information, the study completion date when the planned number of primary endpoint events is achieved, or the date of their death when death is not included in the endpoint.

The time to total HFH events will be tested with an Andersen-Gill model (Table 7) [Andersen, P. K. 1982]. The Anderson-Gill model is an extension of the Cox proportional

hazards model, where the time increments between events will be included in the model to estimate the hazards. Intervention group and the stratification factors used for randomization will be included in the model as fixed effects. Robust standard errors will be used to account for correlations of event times within a participant.

On-treatment Analysis

On-treatment analyses for the primary and secondary efficacy endpoints will be performed as supportive analyses. These analyses will include all randomized participants who have taken at least 1 dose of study intervention (vericiguat or placebo) and will count only those events that occurred during the intervention period. Participants will be analyzed according to the actual intervention received for this analysis. Any participants who received both placebo and vericiguat during the study by mistake will be analyzed according to the planned intervention.

Missing Data

Participants who prematurely discontinue study intervention will be followed for further data collection. As long as the participant does not withdraw consent for any further data collection, every effort will be made to collect at least data on the components of the primary endpoint throughout the study. Therefore, it is expected that the amount of missing data will be minor, as most participants will be followed up until study termination.

For the primary analysis, participants without any HFH or CV death events at the time of analysis will be censored at their last available information or the date of their non-CV death (Table 7). The censoring mechanism is assumed to be noninformative.

Missing data sensitivity analyses will be performed to assess the robustness of the study results. Details will be described in the sSAP.

Table 7 Primary Analysis Strategy for Efficacy Variables

Endpoint	Statistical Method [a]	Analysis Population	Missing Data Approach
Primary Endpoint			
Time from randomization to first event of CV death or HFH	Stratified Log-Rank Test	ITT	Censored at the last available information
Secondary Endpoints			
Time from randomization to CV death	Stratified Log-Rank Test	ITT	Censored at last known alive date
Time from randomization to the first event of HFH	Stratified Log-Rank Test	ITT	Censored at the last available information
Time from randomization to total HFH events (including the first and recurrent events)	Andersen-Gill model	ITT	Censored at the last available information
Time from randomization to first event of all-cause mortality or HFH	Stratified Log-Rank Test	ITT	Censored at last available information
Time from randomization to all-cause mortality	Stratified Log-Rank Test	ITT	Censored at last known alive date

CV=cardiovascular; HFH=heart failure hospitalization; ITT=intention to treat.

[a]Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.

9.6.2 Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory tests, and vital signs.

The analysis of safety results will follow a two-part approach (Table 8): general safety assessment and assessment of safety topics of interest.

General Safety Assessment

The following AEs will be collected for this study: any AE that leads to study intervention dose modification or discontinuation, any AE leading to withdrawal from the study, COVID-19 disease-related AEs, and any ECI or SAE (Section 8.4). The general safety assessment will include summarization of aforementioned AEs and broad AE categories. These safety endpoints will be summarized by frequency (percentage) of participants with specific events.

For continuous measures such as laboratory values and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided.

In addition, descriptive statistics in the above analyses will be supplemented with 95% CIs for between-treatment differences for specific AEs with incidence ≥5% of participants in at least 1 of the intervention groups and AEs by SOC. 95% CIs for between intervention group differences using the Miettinen and Nurminen (M&N) method (1985) [Miettinen, O. and Nurminen, M. 1985] will be provided.

CIs provided as part of the general safety assessment are neither associated with prespecified hypotheses nor adjusted for multiplicity. Therefore, CIs should be regarded as helpful descriptive measures for review of the safety profile, not a formal method for assessing statistical significance of between-group differences.

Assessment of Safety Topics of Interest

Safety topics of interest include AEs of symptomatic hypotension and anemia and laboratory values consistent with potential DILI events (Section 8.4.7). For these safety endpoints, descriptive statistics and CIs for between-group comparisons will be provided.

Table 8 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% CIs[a]
General Safety Assessment	AE Summary[b]	X	
	Specific AEs[b], PDLCs, change from Baseline Results (Laboratory values, Vital Signs)	X	
	Specific AEs[b] (incidence ≥5% of participants in at least one of the intervention groups), AE [b] by SOCs	X	X
Safety Topics of Interest	Symptomatic hypotension	X	X
	Anemia	X	X
	Potential DILI	X	X

AE=adverse event; CI=confidence interval; DILI=drug-induced liver injury; ECI=events of clinical interest; PDLC=predefined limit of change; SAE=serious adverse event; SOC=System Organ Class; X=results will be provided.

a Difference in proportions between groups

b AEs include selected NSAEs (AEs that lead to study intervention dose modification or discontinuation, AEs that lead to discontinuation from the study, COVID-19 disease-related AEs), SAEs, and ECIs.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the intervention groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis testing will be performed on these characteristics. The number and percentage of participants randomized and the primary reason for discontinuation will be displayed. Demographic variables (eg, age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

An efficacy IA is planned when approximately 70% (413) of the planned number of CV death events (590) are observed. Based on the assumptions from the sample size calculation, the IA will take place approximately 31.7 months after the start of the study, shortly after all participants have been accrued and approximately 8 months before the Primary Completion Date. To ensure that the study has accumulated adequate follow-up for safety assessment if stopped for positive efficacy results, the timing of the efficacy IA will also require that the median follow-up time be at least 10 months. Under the assumption of a placebo incidence rate of 6.0 participants with a CV death event per 100 patient-years of follow-up, the median follow-up time when 413 CV death events have been observed is expected to be approximately 15 months. The median treatment duration will be approximately 14 months.

If the study enrollment rate and/or observed incidence rate are substantially higher than anticipated and thus median follow-up time is less than 10 months when 413 CV death events have occurred, the efficacy IA will be delayed until 10 months of median follow-up is achieved. The efficacy IA may become unnecessary if the timing of the IA falls too close to the final analysis. The decision to adjust the timing of or to cancel the efficacy IA will be made by the blinded Sponsor team.

At the efficacy IA, the primary endpoint and the secondary endpoint of time to CV death will be tested. The study can be terminated early for success only if both the primary endpoint and the CV death endpoint are statistically significant based on the prespecified IA boundaries. Otherwise, the study will continue until the prespecified number of CV deaths (590) are accumulated.

The Hwang, Shih and De Cani (γ=-5.4) alpha-spending function [Hwang, I. K. and Shih, W. J. 1990] will be used for the efficacy IA to assess superiority of vericiguat. The spending function can be expressed as

$$f(t) = \alpha\left(\frac{1-e^{-\gamma t}}{1-e^{-\gamma}}\right),$$

with *t* denoting the percentage of information included at the respective IA.

With this alpha-spending approach and a percentage of information of 70%, the nominal significance level will be approximately 0.005 (one-sided) at the IA and 0.024 (one-sided) at the final analysis, respectively. This testing approach controls the one-sided alpha between the efficacy IA and final analysis at 0.025.

The actual alpha to be spent at the efficacy IA will be precisely determined using the number of observed CV death events and the alpha-spending function defined as above. This alpha level will be applied to both the primary endpoint and the CV death endpoint. At the final analysis, the actual alpha to be spent for each endpoint will be determined using the final number of primary endpoint and CV death events using the same spending function.

Assuming hazard ratio for both the primary endpoint and CV death is 0.8, the probability to terminate the study for efficacy at the IA based on the aforementioned stopping rule is approximately 34%.

If the study can be stopped early for success, the nominal one-sided significance level of approximately 0.005 for the primary endpoint and CV death will be applied to other secondary endpoints as well.

If the primary endpoint test is significant at IA but CV death is not, the study will continue until the planned number of CV death events are accumulated. However, the hypothesis testing for the primary endpoint will be considered significant based on the IA. Analysis using the final database will be performed and included in the CSR.

An external DMC will assess the results of the IA and may recommend early study termination if the IA shows clear and consistent benefit of vericiguat as guided by the above described alpha-spending approach.

If the DMC recommendation leads to termination of the study at the IA due to efficacy, all participants will be scheduled for a Final Visit or Final Contact as appropriate. An additional analysis will be performed using the entire data collected up to the study completion, ie, it will also include data collected after the cutoff for the IA. This analysis will not be used to test any hypotheses.

9.8 Multiplicity

The study-wise one-sided alpha level will be controlled at 0.025 for the test of the primary endpoint. Multiplicity due to the IA at 70% of planned primary endpoint events and CV deaths will be controlled using a Hwang, Shih and De Cani (γ=-5.4) alpha-spending function.

Hypotheses H2 and H3 (addressing time to CV death and time to the first HFH), are considered to be supportive endpoints of the primary endpoint. They will be tested only if the test of H1 is successful but will not otherwise be controlled for multiplicity.

The other secondary endpoints, H4, H5, and H6, addressing time to total HFH events, time to all-cause mortality, and time to first event of composite of HFH or all-cause mortality, will be controlled for multiplicity using a hierarchical testing approach. These secondary endpoints will be tested only if the primary composite endpoint is significant at the IA or final analysis. Total HFH events will be tested first, and only if this is significant, the composite of all-cause mortality and HFH will be tested afterwards. All-cause mortality will be tested only if both of the above endpoints are tested significant.

At the IA, if the study is stopped early for efficacy, the secondary endpoints will be tested based on the same alpha as the primary composite endpoint using the aforementioned approach.

9.9 Sample Size and Power Calculations

The sample size estimation is based on a 1:1 randomization and a study-wise one-sided significance level of 0.025. In accordance with the planned IA, the nominal one-sided significance level will be approximately 0.024 at the final analysis. A conservative approach of power calculation based only on the final analysis is used.

This study will be an event-driven study for CV deaths. The sample size calculation is driven by the power for the CV death endpoint and the ability to accumulate the target number of events within a reasonable time frame (39.5 months study duration from first participant randomized to the Primary Completion Date). The relative reduction in risk with vericiguat is assumed to be 20%, corresponding to a HR of 0.8 for CV death endpoint. Based on an expected incidence rate in the placebo group of 6 participants with an event per 100 patient-years of follow-up for CV death (see Section 9.9.1), a sample size of approximately 6000 participants enrolled over approximately 27 months with approximately 39.5 months study duration is expected to accumulate approximately 590 CV deaths. Those event counts will provide 80% power for CV death if a significant result is observed for the primary endpoint.

The incidence rate in the placebo group of the primary endpoint is expected to be 11.5 participants with an event per 100 patient-years of follow up. The relative risk reduction with vericiguat is assumed to be 20%, relating to a HR of 0.8. With a sample size of 6000 participants, it is expected that 1080 participants with a primary endpoint event will be observed and there will approximately be 95% power for primary hypothesis testing. The time point of final analysis will be based on the number of CV deaths events, and the total number of participants with primary endpoint event may vary depending on the actual event rate in the study.

If the study is not stopped early for success, the median follow-up time (including off-treatment time) is expected to be approximately 22.5 months.

9.9.1 Rationale for Incidence Rate Assumption

The estimated incidence rates for the primary endpoint and for CV death in the placebo arm are based on incidence rates in PARADIGM-HF and DAPA-HF. In PARADIGM-HF, the incidence rate for the composite of CV death or HFH was ~10.5 participants with an event per 100 patient-years of follow-up in the sacubitril/valsartan and ~13.2 participants with an event per 100 patient-years of follow-up in the enalapril arms [Srivastava, P. K., et al 2018]. For CV death, the rates were approximately 6 and 7.5 participants with an event per 100 patient-years of follow-up, respectively. In DAPA-HF, the incidence rates for the composite of CV death or HFH were 11.4 and 15.3 participants with an event per 100 patient-years of follow-up in the dapagliflozin and placebo arms, respectively. For CV death, the incidence rates were 6.5 and 7.9 participants with an event per 100 patient-years of follow-up in the dapagliflozin and placebo arms, respectively [McMurray, J. J. V., et al 2019]. Both studies included patients who had an HFH within 6 months of randomization, so incidence rates for this study are expected to be lower. Detailed incidence rates for those without a HFH within 6 months are not available; however,

based on available data from those with and without a prior HFH at any point prior to enrollment in PARADIGM-HF and those with and without a HFH within 1 year prior to enrollment in DAPA-HF, the incidence rate for the primary endpoint in the placebo arm of this study is estimated to be 11.5 participants with an event per 100 patient-years of follow-up.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables in all participants:

- Age (<65 years vs ≥65 years)
- Sex (female vs male)
- Geographic region (Eastern Europe / Western Europe / North America / Latin and South America / Asia Pacific)
- eGFR at randomization (15 to 30 mL/min/1.73 m^2 vs >30 to 60 mL/min/1.73 m^2 vs >60 mL/min/1.73 m^2)
- NYHA class at baseline (II vs III/IV)
- Ischemic heart disease at baseline, defined as history of 1 or more of the following conditions: CAD, MI, PCI, and/or CABG
- Use of an ARNI at baseline
- Use of SGLT2i at baseline
- Presence of ICD therapy at baseline
- Baseline NT-proBNP (by Quartiles)
- Baseline LVEF (< median, ≥ median)
- Race (White / Black / Asian / Other)

9.11 Compliance (Medication Adherence)

Percent compliance will be calculated according to the following formula and summarized using descriptive statistics.

$$\text{Compliance (\%)} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days in the Intervention Period}} \times 100.$$

Deviations from protocol-directed administration will be summarized at the end of the study.

9.12 Extent of Exposure

The extent of exposure will be summarized as the duration of study treatment. Furthermore, an exposure summary based on dosage and dose titration will also be provided.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors using a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Pursuant to Union law (Clinical Trials Directive 2001/20/EC and Clinical Trials Regulation 536/2014), the Investigator is responsible for pseudonymizing and assigning a key-code/patient ID to each study subject. In addition, the Investigator is required by Union law to store the Key (linking the Patient ID to the full name of the study subject) at the site in the EU/EEA throughout the course of the study and for a designated period of time thereafter. Finally, the study site is only permitted to share pseudonymized study subject personal data with the Sponsor.

The European Data Protection Board, in its Recommendations 01/2020 on measures that supplement transfer tools to ensure compliance with the EU level of protection of personal data ("Recommendations"), states in Paragraph 85 that pseudonymization (of study subject) personal data under the conditions described above constitutes an effective supplemental measure.

Organizational measures are contractually imposed on third party vendors wherever possible, to ensure that Personal Data are protected by industry-best practices against accidental destruction or loss (physical/logical) which include regular backup procedures, Firewalls, and disaster recovery plans.

In support of Corporate Policy 1 Information Risk Management, on a Sponsor-wide basis all supplier relationships, both IT and non-IT related, are strongly encouraged to meet the Sponsor's Supplier Information Risk Management Standard. To protect the confidentiality, availability and integrity of Sponsor information, conformity to information risk requirements by supplier personnel, hardware and software may be measured, analyzed and appropriate corrective/preventive actions taken as necessary. Based on the supplier criticality, additional activities (e.g., on-site reviews, integrated business continuity exercises) may be required to ensure the cyber-resiliency of the supplier on an on-going basis.

The Sponsor has implemented (Corporate Policy 13.1 Information Security Standards Handbook) an organization-wide process to assign user access rights based on the whether the employee/contractor has a legitimate need to utilize a database in order to carry out his/her job; manager approval is required when granting user access rights (beyond those sites or databases intended for all employees/contractors); and a process is in place for an annual review by each manager of the user access rights currently in place. Organizational measures, also contractually imposed on third party vendors, to prevent data processing systems from being used by unauthorized persons include i) user identification and authentication procedures (e.g., special characters, minimum length, regular change of password), and ii) automatic blocking (e.g., password or timeout).

The Sponsor utilizes a database called "InForm", operated by Oracle, for the storage of its study subject clinical trial data. InForm is a role-based system and only authorized users can see the data. Sites may only see the data they have entered. Access by Sponsor users is restricted to only those associated with a specific clinical trial.

Study sites are provided with a password to access the database. Access to InForm requires https (Secure Socket Layer) with a FIPS 140-2 compliant algorithm to connect to the application via the study site's web browser. Once logged into the system, the connection between the database, located in Ashburn, Virginia, USA, and the site, is encrypted. The Sponsor also stores the name and access credentials of the Investigators and other site staff (Study Coordinators) who record patient data into InForm. Such study staff personal data is not pseudonymized. Note, such encryption during transmission may not meet all conditions imposed by the EDPB in its Recommendations for this encryption, on its own, to constitute an effective supplemental measure.

Data, whether concerning a study subject or site staff, stored in the InForm database is encrypted. Note, such encryption may not meet all conditions imposed by the EDPB in its Recommendations for this encryption, on its own, to constitute an effective supplemental measure.

Whenever possible, organization wide measures are imposed on third party vendors to prevent unauthorized persons from gaining access to the data processing systems available on premises and in facilities (including databases, application servers and related hardware), where Personal Data are processed, include i) Access control system (ID reader, chip), ii) key management, card-keys procedures, and iii) on-site security personnel and alarm system.

InForm is a HIPAA Part 11 capable system. Any data entered/changed or deleted will be associated with a viewable audit trail.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20). Pursuant to organization-wide requirements, the Sponsor periodically conducts audits of the vendors providing IT services, including Oracle, the vendor supporting the InForm database. The most recent audit of Oracle and its operations of InForm occurred in May 2020. Finally, Oracle has obtained ISO 27001 certification for the various databases it offers to third parties as a service, including the InForm database.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Steering Committee

This study will be conducted in consultation with a Steering Committee. The Steering Committee is comprised of:

Sponsor personnel,

Investigators participating in the study, and

Consulting therapeutic-area experts and clinical trialists.

The Steering Committee will provide guidance on the operational aspects of the study and make recommendations to the EOC.

Specific details regarding responsibilities and governance of the Steering Committee will be described in a separate charter.

10.1.4.2 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management and an external cardiologist. The EOC will receive and decide on any recommendations made by the DMC and Steering Committee regarding the study.

10.1.4.3 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the external collaborating organization protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.4 Clinical Events Committee (CEC)

A CEC will evaluate the following events for the purposes of confirming them according to the criteria in Section 9, as well as evaluating the presence of confounding factors.

1. Death

2. CV hospitalizations

3. UHF visits

The CEC will be comprised of qualified members, who are not investigators in the study and are not otherwise associated with the Sponsor. The adjudication guidance and clinical endpoint definitions are described in detail in the CEC charter.

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

10.1.4.5 National Leader Committee

The primary role of the National Leader Committee is to serve as the interface between the Steering Committee and the study sites to facilitate the progress of the study at the regional level. The National Leader Committee is composed of Country Leads selected by the Sponsor from the investigators in each country with appropriate clinical study experience. National Leader Committee members should participate with their local study site to ensure adequate direct experience with the study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as

Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- Visit 1/Screening laboratory tests (Section 1.3.1) may be performed at a local laboratory, central laboratory, or by Point of Care device. Historical results collected within 30 days before randomization are also acceptable.

- After screening, the tests detailed in Table 9 will be performed by the central laboratory. If extenuating circumstances prevent submission of samples to the central laboratory, a local laboratory may be used for protocol-required laboratory assessments, with the exception of NT-proBNP. The local laboratory results must be entered into the eCRF.

  NOTE: As NT-proBNP results are expected to remain blinded during the treatment period (after first dose of study intervention), protocol-specified NT-proBNP tests must not be performed at local laboratories.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5. Screening laboratory assessments may be performed at the local laboratory.

  NOTE: Central laboratory testing may be used once during screening.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="6">Hematology</td><td colspan="2">Platelet Count</td><td colspan="2" rowspan="4">RBC Indices:
MCV
MCH
MCHC
RDW</td><td rowspan="6">WBC count with Differential
(%, absolute counts):
Neutrophils (Total)
Immature granulocytes
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="2">RBC Count</td></tr>
<tr><td colspan="2">Hemoglobin</td></tr>
<tr><td colspan="2">Hematocrit</td></tr>
<tr><td colspan="2">MPV</td><td colspan="2">Reticulocytes</td></tr>
<tr><td colspan="4">Nucleated RBCs</td></tr>
<tr><td rowspan="3">Chemistry</td><td>Sodium</td><td>Chloride</td><td>Bicarbonate</td><td>Potassium</td></tr>
<tr><td>BUN</td><td>Creatinine (eGFR)</td><td>Uric Acid</td><td>Calcium</td></tr>
<tr><td colspan="4">Glucose (fasting is not required)</td></tr>
<tr><td rowspan="2">Liver Function Tests</td><td>Alkaline phosphatase</td><td>ALT/SGPT</td><td>AST/SGOT</td><td>GGT</td></tr>
<tr><td colspan="2">Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)</td><td colspan="2">Albumin</td></tr>
<tr><td>Other</td><td colspan="4">NT-proBNP</td></tr>
<tr><td>Pregnancy Testing</td><td colspan="4">Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">FSH (as needed in WONCBP only)</td></tr>
<tr><td colspan="5">ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; MPV=mean platelet volume; NT-proBNP=N-terminal pro-brain natriuretic peptide; RBC=red blood cell; RDW=red cell distribution width; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

Notes:
Urea is acceptable if BUN is not available per institutional standard.
Liver Function tests include ALT/SGPT, AST/SGOT, alkaline phosphatase, albumin, GGT, and total bilirubin.
eGFR will be calculated using the CKD-EPI formula.
Urine pregnancy testing and other screening tests may be performed by the local laboratory.</td></tr>
</table>

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

NT-proBNP results that could unblind the study will not be reported to investigative sites or other blinded personnel after Visit 2 until the study has been unblinded.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Selected nonserious AEs, SAEs, and other reportable safety events will be reported by the sites.

Additional country-specific requirements for adverse event reporting are described in Appendix 7.

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

Selected NSAEs are nonserious AEs that meet any of the following criteria:

- AEs that lead to study intervention dose modification or discontinuation
- AEs that lead to withdrawal from the study
- COVID-19 disease-related AEs

Additional country-specific requirements for adverse event reporting are described in Appendix 7.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

Selected nonserious AEs, SAEs, and other reportable safety events will be reported by the sites.

Additional country-specific requirements for adverse event reporting are described in Appendix 7.

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
    - Yes, there is a reasonable possibility of Sponsor's product relationship:
        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
    - No, there is not a reasonable possibility of Sponsor's product relationship:
        - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

Selected nonserious AEs, SAEs, and other reportable safety events will be reported by the sites.

Additional country-specific requirements for adverse event reporting are described in Appendix 7.

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent.

Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Requirements for Germany

For sites participating in Germany all NSAEs must be reported to the Sponsor.

This revision applies to the following sections:

- Section 4.2.1.2 – Safety Endpoints
- Section 8.4 – Adverse Events, Serious Adverse Events, and Other Reportable Safety Events
- Section 8.4.1 – Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information
- Section 8.4.3 – Follow-up of AE, SAE, and Other Reportable Safety Event Information
- Section 10.3 – Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting
- Section 10.3.2 – Definition of AE
- Section 10.3.5 – Recording AE and SAE
- Section 10.3.6 – Reporting of AEs, SAEs, and Other Reportable Events to the Sponsor

10.7.2 Country-specific Requirements for China

Sites participating in China will not collect specimens for planned genetic analysis, exploratory biomarker research, and future biomedical research.

This applies to the following sections:

- Section 4.2.1.4.1 – Planned Genetic Analysis
- Section 4.2.1.5 – Future Biomedical Research
- Section 8.8 – Biomarkers
- Section 8.9 – Future Biomarker Sample Collection

10.7.3 Country-specific Requirements for South Korea

An additional clinic visit will be performed for all participants in South Korea between study visits V4 (Day 28 ± 4 days) and V5 (Week 24 ± 14 days). This additional clinic visit will be conducted as an unscheduled visit and should occur anytime 2 to 8 weeks after V4.

This applies to Section 1.3.1 – Schedule of Activities-All Participants.

10.8 Appendix 8: Determination of ALBI Grade

The ALBI Grade is based on a linear score calculated using the values for blood albumin and bilirubin in the following formula:

$ALBI_{SCORE} = (\log_{10}[\text{bilirubin}] \times 0.66) + (\text{albumin} \times -0.085)$ where albumin is in g/L and bilirubin in µmol/L [Johnson, P. J., et al 2015].

ALBI Grade	$ALBI_{SCORE}$
1	≤ -2.60
2	-2.59 to -1.39
3	> -1.39

Calculation of the ALBI Grade maybe facilitated by use of online medical calculators (https://www.mdcalc.com/albi-albumin-bilirubin-grade-hepatocellular-carcinoma-hcc).

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ACCF	American College of Cardiology Foundation
ACEI	angiotensin-converting enzyme inhibitor
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AHA	American Heart Association
ALBI	albumin to bilirubin ratio
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ARB	angiotensin II receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
AST	aspartate aminotransferase
BP	blood pressure
CABG	coronary artery bypass grafting
CEC	Clinical Events Committee
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CRF	Case Report Form
CRT	Cardiac resynchronization therapy
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CV	cardiovascular
DAPA-HF	Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction
DEGs	Data Entry Guidelines
DILI	drug-induced liver injury
DMC	Data Monitoring Committee

Abbreviation	Expanded Term
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EQ-5D	EuroQol Group 5-Dimensional questionnaire
EQ-5D-5L	EuroQol Group 5-Dimensional, 5-level questionnaire
EQ VAS	EuroQol Group Visual Analog Scale
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	First site ready
GCP	Good Clinical Practice
GDMT	guideline-directed medical therapy for heart failure
hCG	human chorionic gonadotropin
HF	heart failure
HFH	heart failure hospitalization
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis(ses)
IB	Investigator's Brochure
ICD	implantable cardioverter-defibrillator
ICF	Informed Consent Form

Abbreviation	Expanded Term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intention to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	interactive voice response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAM	lactational amenorrhea method
LVEF	left ventricular ejection fraction
M&N	Miettinen and Nurminen method
MRA	mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NO	nitric oxide
NSAEs	nonserious adverse event
NSTEMI	non-ST elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PCI	percutaneous coronary intervention
PDE5	phosphodiesterase type 5
PK	pharmacokinetic
QD	Once daily
QoL	quality of life
RNA	ribonucleic acid

Abbreviation	Expanded Term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
sGC	soluble guanylate cyclase
SGLT2i	sodium-glucose cotransporter 2 inhibitor
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOC	System Organ Class
sSAP	supplemental Statistical Analysis Plan
STEMI	ST elevation myocardial infarction
SUSAR	suspected unexpected serious adverse reaction
TIA	transient ischemic attack
UHF	urgent heart failure
ULN	upper limit of normal
VAS	Visual Analog Scale
VICTOR	**V**er**IC**igua**T** Gl**O**bal Study in Participants With Chronic Heart Failure With **R**educed Ejection Fraction
VICTORIA	**V**er**IC**igua**T** Gl**O**bal Study in Subjects With Heart Failure With **R**educed Eject**I**on Fr**A**ction
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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